Good results from combining etanercept to prevailing DMARD therapy in refractory juvenile idiopathic arthritis

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ABSTRACT

Objective. *To assess the effect of etanercept added to prevailing drug therapy in patients with juvenile idiopathic arthritis (JIA) whose disease was refractory to conventional disease-modifying antirheumatic drug (DMARD) treatment, including combinations of different DMARDs.*

Methods. *Data on 31 JIA patients with a disease resistant to conventional DMARD treatment were retrospectively collected from medical records and assessed for a one-year period after the introduction of etanercept or to the time of cessation of the drug due to a lack of efficacy or side effects. Efficacy was assessed based on the normal laboratory indexes of inflammation and changes in the following parametres: number of DMARDs used and intra-articular (i.a.) glucocorticoid injections. The numbers of inpatient days needed were also recorded.*

Results. *Etanercept was well tolerated. Only two patients stopped discontinued the treatment because of allergic rash, after 3 weeks of treatment in one case and after 4 months in another. In two cases the treatment was discontinued because of a lack of efficacy. During the treatment, there was a significant decrease in the number of DMARDs used and the i.a. glucocorticoid injections needed as well as in the dose of per oral glucocorticoids. The laboratory parameters also improved. In addition, there was a significant decrease in the number of inpatient days per 3-month period before and during the etanercept treatment.*

Conclusion. *The addition of etanercept to conventional DMARD therapy in children with the most severe cases of JIA leads to an excellent clinical response during the first 12 months. The tolerability of the drug is good in combination therapy with various DMARDs.*

Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous disease with a spectrum from pauciarticular non-deforming disease to polyarticular destructive disease prone to severe manifestations, such as amyloidosis, need for total joint replacement surgery, osteoporosis and retarded growth (1). Though the prognosis seems now better than some decades ago, especially thanks to more active use of methorexate (mtx), there are still cases resistant to conventional disease-modifying antirheumatic drug (DMARD) therapy. In such instances, tumor necrosis factor (TNF)-blockers may be useful.

Etanercept is a biologic response modifier that binds the cytokines TNF and lymphotoxin-α, thus blocking their interaction with cell-surface receptors (2). Etanercept is a genetically engineered fusion protein consisting of two p75-soluble TNF receptor molecules fused to the Fc fragment of human immunoglobulin G_1.

There are scant published data on the clinical use of etanercept in JIA. A two-part, multicenter trial of etanercept in children with active polyarticular juvenile rheumatoid arthritis (JRA) refractory or intolerant to mtx therapy reported etanercept to be effective and well tolerated (3). The patients represented all of the three major onset types. In the first part of the study, where all patients received open-label etanercept at 0.4 mg/kg subcutaneously twice weekly for 90 days,74% achieved the JRA definition of improvement. In the double-blind part of the study, where the responders were randomized to either placebo or etanercept, a significant difference was seen in the disease flare frequency between the groups, with percentages of 81% and 28%, respectively. There were no significant differences between the two treatment groups in the frequency of adverse reactions, injection site reactions being most common in the active group.

We have three years' experience of the clinical use of etanercept in the treatment of JIA. The results reported here are retrospective data on the effect and safety of the compound in the treatment of active JIA refractory to conventional drug treatment. Our treatment schedule was to use etanercept in combination with the prevailing DMARD therapy.

Patients and methods

According to the statistics of the

Finnish Social Insurance Institute, the total number of children with JIA is approximately 1,200 in the population of about one million children in Finland. The care of patients with JIA in Finland is strongly centralised to the Rheumatism Foundation Hospital (RFH), which means that almost all severe cases of JIA in the country are under our supervision.

Since the spring of 1999, there has been a possibility to receive etanercept in Finland. At that time, the first children with the most severe JIA were chosen for the treatment. There is a total of 31 JIA patients who have started etanercept treatment between April 1999 and September 2000 in our hospital. We report retrospectively collected data on the results of the therapy.

The series consisted of 23 girls and 8 boys. The mean age at the start of the treatment was 9.9 years (range 3 - 15) and the duration of the disease was 6.4 (range 0.8 - 13.6) years. The commonest diagnosis was polyarthritis (in 22 children), while 6 patients had extended oligoarthritis and 3 systemic onset disease (Table I).

The mean number of current DMARDs used was 2.6 (range 1 – 4). All patients had received mtx during their disease course, and 26 patients were still taking it at the beginning of the study. The maximum dose of mtx was 30 mg/m^2/week. The mean dose of *per oral* corticosteroid was 16 (range 0 – 40) mg of prednisolone every other day. All the patients continued their earlier treatment (Table II) until inflammatory activity was strongly reduced or remission was attained. Thereafter, the conventional treatment was gradually reduced.

The mean number of i.a. corticosteroid injections calculated from the 3-month period before the introduction of etanercept was 8. During the study, glucocorticoid injections were given at the routine hospital visits or between them if necessary, and for this retrospective analysis, the number of i.a. injections needed was recorded as an indicator of treatment effect (4).

At the baseline of the etanercept treatment, all patients had active disease. The mean erythrocyte sedimentation rate (ESR) was 40 mm/h and the mean C-reactive protein (CRP) was 25 mg/l (Fig. 1).

The patients received etanercept with a standard dose of 0.4 mg/kg of body weight twice a week. They were seen in the RFH paediatric ward by a paediatric rheumatologist at least every three months. The standard laboratory tests, i.e., ESR, CRP, blood count, liver enzymes and fS-urea were made at every hospital visit.

Table I. Baseline demographic and clinical characteristics of 31 patients with JIA.

Characteristics	
Sex:	
Girls, n (%)	22 (71)
Boys, n (%)	9 (29)
Mean age (range), years	9.6 (3 – 15)
Diagnosis	
Extended oligoarthritis, n (%)	6 * (19)
Seronegative polyarthritis, n (%)	22 (71)
Systemic onset disease, n (%)	3 (10)
Mean disease duration (range), years	6.3 (0.8 – 13.6)
Number of patients with uveitis (%)	12 (39)

*One patient had antinuclear antibody-positivity.

Table II. Data on the baseline drugs of the patients.

Therapy	No.	(%)
Drugs:		
Hydroxychloroquine	14	(45)
Cyclosporin	21	(68)
Injectable gold	4	(13)
Azathioprine	12	(39)
Sulphasalazine	2	(6)
Methotrexate	27	(87)
Podophyllotoxin	2	(6)
Prednisolone (every 2nd day)	30	(97)
Strategy:		
No drugs	0	(0)
DMARD alone	0	(0)
One DMARD with prednisolone	3	(10)
Prednisolone alone	0	(0)
DMARD combination	1	(3)
DMARD combination with prednisolone	27	(87)

Statistical analysis

The analysis of the efficacy of treatment was based on an intention-to-treat (ITT) analysis with the last observation carried forward (LOCF). A statistical comparison of the changes in the outcome measurements was performed by using Kornbrot's rank difference test and the Friedman two-way analysis of variance by ranks. The most important descriptive values were expressed with a rank-based 95% confidence interval (CI) for difference in paired medians. The α level was set at 0.05 for all tests.

Results

Etanercept was well tolerated. Two patients had recurrent urticaria-like reactions after the etanercept injections, which necessitated cessation of the treatment after three weeks in one case and after four months in another (5). Some other patients had minor side effects, which did not, however, necessitate cessation of the treatment. The drug was discontinued in two patients due to inefficacy, after three months in one and after six months in another. In addition, one patient was admitted to another hospital nearby her place of residence after 9 months' follow-up. Furthermore in one patient the treatment was changed to infliximab after four months due to difficulties to carry out the etanercept injections at home.

The beneficial effect of etanercept on the activity of the disease was already seen at the 3 months' control (Fig. 1). The median value of ESR (mm/h) and that of CRP (mg/l) decreased from 34 to 14 and from 13 to 1, respectively. During the same period, it was possible to cut down the median dosage of per oral corticosteroids equivalent to prednisolone every second day from 10 to 7.5 mg. Overall six patients were able to stop corticosteroids during the trial. The median (95% confidence interval) change in the number of DMARDs during the follow-up was -1 (-0.5 to -1.0). Mtx dose could be decreased in eight patients by a mean of 5 mg, from 25 to 20 mg. The median number of i.a. corticosteroid injections per 3 months was reduced from 8 to 1 injections. These beneficial effects were stable

during the follow-up period of 12 months (Table III). In addition, there was a marked decrease in the number of hospitalisation days assessed from the consecutive 3-month periods before the start of the therapy to the end of the follow-up (median 8.0 and 3.0, respectively).

No clear-cut effect was found on the course of the eye disease in the 12 patients with uveitis. Two patients out of the 12 experienced an activation of their uveitis during the follow-up.

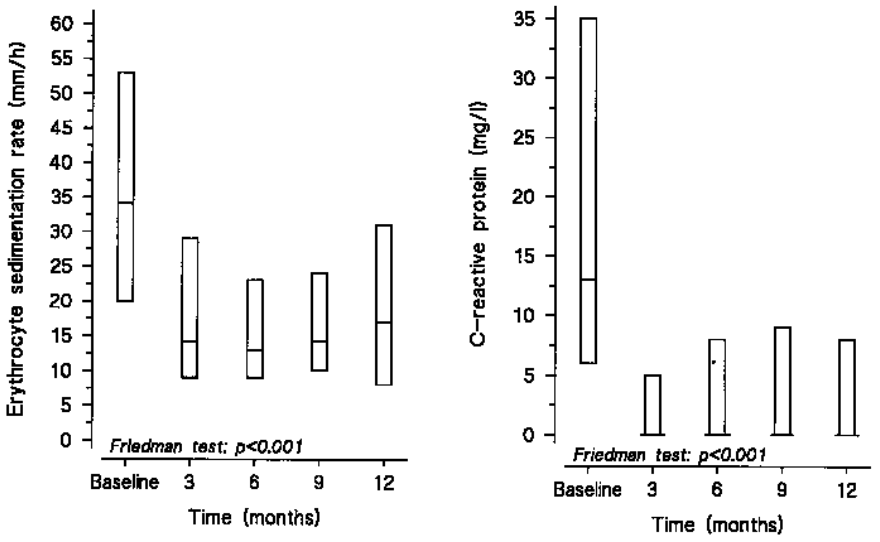

Fig. 1. Treatment response estimated by ESR and CRP during a follow-up of 12 months in 31 JIA patients. In the box plot model, the horizontal line in the middle of the bar represents median and the lower and upper boundaries the 25th and 75th percentiles, respectively. Upper normal limits for ESR and CRP are 12 mm/h and 10 mg/l, respectively.

Discussion

The present series included the most severe cases of JIA. All the patients had been treated with several DMARDs and with different drug combinations without achieving acceptable disease control. Against that background, the effect of etanercept on the outcome measurements used – laboratory indexes of inflammation, number of i.a. glucocorticoid injections given and inpatient days needed was excellent, with statistically significant improvements during the follow-up. Due to our active treatment policy, the number of i.a. glucocorticoid injections in this retrospective series can be considered as comparable to the number of swollen joints (4). During the one-year follow-up, there was also a clear trend towards a reduction of the number of DMARDs and the dose of per oral corticosteroids needed.

In addition to the efficacy of etanercept in this clinical series, it is to be noted that no serious side effects were seen, though we added the compound to the prevailing DMARD drug therapy.

There are some reports on the improving outcome of JIA during the last decade including our own experience (6). The result can been speculated to be due to an increasing use of cytostatic drugs. Nowadays there is a consensus to treat JIA aggressively, with mtx up to a weekly dose of 30 mg/m^2 as the gold standard, a schedule which has shown satisfactory results in 60-80% of patients (7). However, there are still cases whose disease cannot be controlled with conventional DMARDs. In such instances, which made up our present series, etanercept is the drug of choice (8).

It is to be noted that the mean disease duration in our series was over 6 years, which means that many of our patients with active disease had been waiting for an effective drug for years. In such cases, it is naturally optimal to start TNF blockers earlier in the disease course.

In conclusion, according to our present retrospective analysis, combination of etanercept to the prevailing DMARD treatment seems well-tolerated and effective for patients with JIA resistant to conventional therapy

References

1. ZAK M, PEDERSEN FK: Juvenile chronic arthritis into adulthood:A long-term follow-up study. *Rheumatology (Oxford)* 2000; 39: 198-204.
2. Package Insert. Enbrel (etanercept). Seattle, WA, Immunex Corporation, June 2000.
3. LOVELL DJ, GIANNINI EH, REIFF A *et al.*: Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med* 2000; 342: 763-9.

Table III. Improvement according to individual outcome variables. Intent-to-treat analysis with LOCF.

Variable	Baseline Median (IQR)		End point Median (IQR)		Median change[3] Median (95% CI)		p-value[4]
Prdn, dose[1], mg	12.5	(10.0-20.0)	7.5	(5.0-15.0)	-5.0	(-2.5 to -7.5)	< 0.001
DMARDs, n	3	(2-3)	2	(1-2)	-1	(-0.5 to -1.0)	< 0.001
GC injections[2], n	8	(3-11)	1	(0-3)	-6	(-3 to -9)	< 0.001
ESR, mm/h	34	(19-53)	17	(8-32)	-15	(-8 to -21)	0.001
CRP, mg/l	8	(6-35)	0	(0-11)	-8	(-2 to -18)	0.012

[1]Dose of prednisolone every 2nd day; [2]calculated within 3-month periods; [3]rank-based confidence interval for difference in paired medians; [4]Kornbrot's rank difference test.
Upper normal limits for ESR and CRP are 12 mm/h and 10 mg/l, respectively.

4. HAAPASAARI J, KAUTIAINEN H,HAKALA M: Effect of combining cyclosporine to prevailing antirheumatic drug therapy in the treatment of juvenile idiopathic arthritis (Letter to the editor). *Clin Exp Rheumatol* 2002; 20: 259.
5. SKYTTÄ E, POHJANKOSKI H, SAVOLAINEN A: Etanercept and urticaria in patients with juvenile idiopathic arthritis. *Clin Exp Rheum - atol* 2000; 18: 533-4.
6. SAVOLAINEN HA, ISOMÄKI HA: Decrease in the number of deaths from secondary amyloidosis in patients with juvenile rheumatoid arthritis. *J Rheumatol* 1993; 20: 1201-36.
7. ILOWITE NT: Current treatment of juvenile rheumatoid arthritis. *Pediatrics* 2002; 109: 109-15
8. MARTINI A: Etanercept improves active polyarticular juvenile rheumatoid arthritis. *Clin Exp Rheumatol* 2001; 19: 122-4.